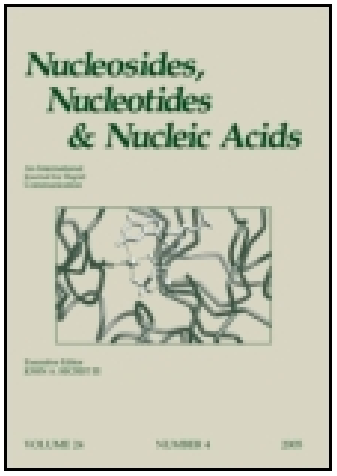

Nucleosides, Nucleotides and Nucleic Acids

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Published online: 10 Dec 2007.

To cite this article: Roland Messer, Cyril A. Fuhrer & Robert Häner (2007) Transformation of D-(-)-Ribose into a Natural Product-Like Scaffold via a Lewis Acid Catalyzed Intramolecular Hetero-Diels-Alder Reaction, Nucleosides, Nucleotides and Nucleic Acids, 26:6-7, 701-704, DOI: 10.1080/15257770701490704

To link to this article: http://dx.doi.org/10.1080/15257770701490704

Nucleosides, Nucleotides, and Nucleic Acids, 26:701–704, 2007

ISSN: 1525-7770 print / 1532-2335 online
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TRANSFORMATION OF D-(-)-RIBOSE INTO A NATURAL PRODUCT-LIKE SCAFFOLD VIA A LEWIS ACID CATALYZED INTRAMOLECULAR HETERO-DIELS-ALDER REACTION

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□ *Starting from D-(-)-ribose, a tricyclic natural product-like scaffold suitable for combinatorial derivatization was synthesized via an intramolecular hetero-Diels-Alder reaction. Lithium perchlorate was found to enhance the reaction rate and, at the same time, had a pronounced influence on the chemoselectivity of the reaction. The stereochemical course of the reaction, however, was not influenced by the Lewis acid.*

Keywords Lewis acid; Hetero-Diels-Alder reaction; bi- and tricyclic structures

INTRODUCTION

The hetero-Diels-Alder reaction has been proven extremely successful in the construction of heterocyclic six-membered rings.[1] In previous work aiming at the construction of natural product like scaffolds, we made use of intramolecular hetero-Diels-Alder reactions to synthesize bi- and tricyclic structures.[2] Thus, compound **1** is tranformed by cyclization at 100°C in toluene within 24 hours into compound **2** in 45% yield (Scheme 1). The moderate yield is the consequence of an elimination reaction leading to product **3**. The formation of this undesired product proceeds most likely via a thermal *syn* elimination pathway,[3] rendering up to 40% of the side material. Exploratory experiments showed that at lower reaction temperatures the elimination process is overproportionally reduced compared to the desired cyclization reaction. The rate and selectivity of Diels-Alder reactions can be increased drastically by the use of Lewis acids.[4] Lithium perchlorate in diethylether (LPDE) has gained particular interest as a powerful medium for Diels-Alder reactions.[5,6] On the other hand, reports describing similar effects by Lewis acids in hetero-Diels-Alder reactions are sparse. To our

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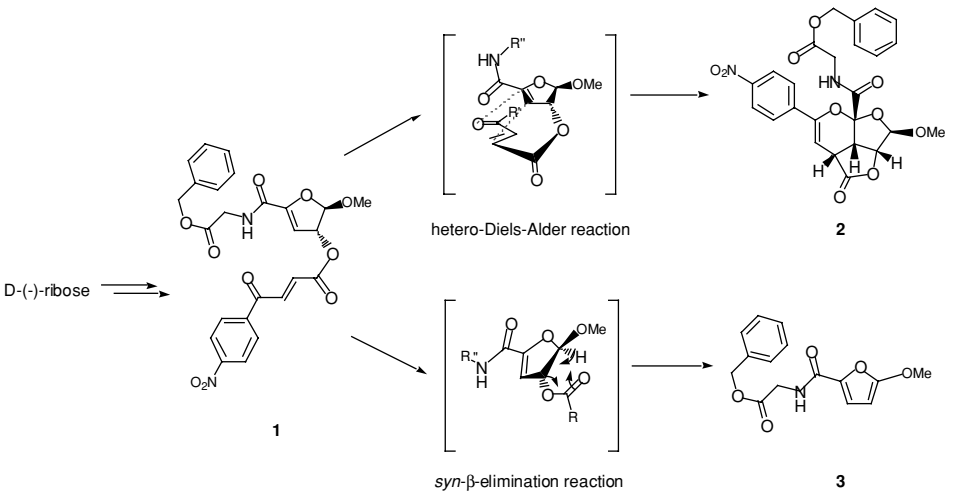

SCHEME 1 Intramolecular cyclization of compound **1** via hetero-Diels-Alder reaction leading to product **2** and formation of the furan **3** via elimination reaction.

knowledge, only three reports exist in which Lewis acid catalysis of hetero-Diels-Alder reactions has been investigated—two involving an oxadiene[6,7a] and one describing the reaction of a nitroso dienophile.[7b] For all reactions, including one example of an intramolecular hetero Diels Alder reaction,[7a] a significant acceleration by LPDE was observed. Since the examples with the oxadiene system[6,7a] are related to the hetero-Diels-Alder of the present work, we explored the influence of lithium perchlorate on the rate as well as the selectivity of the reaction shown in Scheme 1.

In preliminary experiments we tested the influence of different Lewis acids ($LiClO_4$, $Mg(ClO_4)_2$, $Ti(O\text{-}iso\text{-}Pr)_4$, $TiCl_4$) in different solvents on the course of the cyclisation of **1**. The use of lithium perchlorate in acetonitrile showed the best results. This Lewis acid was, therefore, further investigated

TABLE 1 Influence of lithium perchlorate on the course and reaction rates of the intramolecular hetero-Diels-Alder reaction of **1**

Entry	Conditions	$[LiClO_4]$, M	Ratio **1**/**2**/**3**	$k_1 \times 10^6$, s^{-1}	Isolated yield of **2** (%)[a]
1	toluene/100°C/24 h	0	0/53/47	100	45
2	CH_3CN/50°C/72 h	0	10/55/33	8.0	—[b,c]
3	"	0.01	—[b,c]	7.9	—[b,c]
4	"	0.1	12/74/9	8.4	—[c]
5	"	0.5	2/91/7	15.6	—[c]
6	"	1.5	0/95/5	34.9	55

[a]After 72 hours.
[b]Several major byproducts were formed under these conditions.
[c]Not determined.

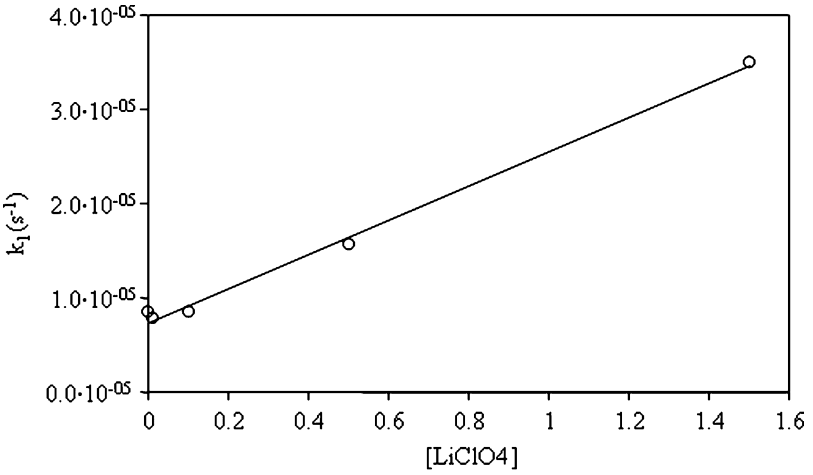

FIGURE 1 Reaction rates of the intramolecular hetero-Diels-Alder reaction shown in Scheme 1 against the lithium perchlorate concentration. (For conditions see Table 1.)

at a reaction temperature of 50°C. The effect of different concentrations of lithium perchlorate in acetonitrile was monitored by NMR analysis at different times (5, 12, 24, 48, and 72 hours).* The proportions of starting material and products over the course of the reaction were determined by integration of the corresponding signals. From these measurements the first order rate constant for the reaction at different lithium perchlorate concentrations was calculated (Table 1). The data show a linear dependence between the lithium perchlorate concentration and the reaction rate (Figure 1). At a concentration of 1.5 M, the highest concentration of lithium perchlorate possible in acetonitrile, a four-fold increase in the rate was observed compared to the uncatalysed reaction at 50°C. Under the so optimized conditions, **2** was isolated in a 55% yield** while the amount of the elimination side reaction **3** was reduced to 5% compared to 33% in the absence of the Lewis acid.

In conclusion, we have described the Lewis acid catalysis of an intramolecular hetero-Diels-Alder reaction. Using lithium perchlorate in acetonitrile as the reaction medium, a rate increase by a factor of four was obtained compared to the uncatalyzed reaction. A competing elimination side reaction was almost entirely suppressed. The use of lithium perchlorate had no influence on the stereochemical course of the reaction.

*In toluene as a solvent, the reaction shows no conversion at 50°C.

Synthesis of ester **2: To a solution of **1** (100 mg, 0.19 mmol) in acetonitrile (5 ml), lithium perchlorate (798 mg, 7.5 mmol) was added. The glass vial was sealed and held at 50°C (internal temperature) for 72 hours. The mixture was worked up as described above and purified by column chromatography (diethylether/$CHCl_3$/hexane 2:2:1) to give 55 mg, (55%) of **2**.

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